

## REMARKS

### Rejection under 35 USC §103

Claims 1-4, 6-13, 12 and 15-18 have been rejected under 35 USC §103(a) as being anticipated by Richardson et al. (US 5,490,980) in view of Green et al. (US 5,525,336); Kanebo Ltd. (JP 02-204407, abstract) Dane, Hair Chemistry 1, and the record for transglutaminase from BRENDA. The office action states, in pertinent part, that :

Richardson discloses a method of cross-linking human keratin proteins, including those found in hair, by applying a composition comprising an effective amount of transglutaminase to hair. Richardson also discloses a method of covalently bonding an alkyl amine moiety, such as in lysine, to a glutamine residue, both of which are contained in the keratin of hair, by contacting the hair with a composition comprising an effective amount of a transglutaminase...The source of the transglutaminase may be mammalian or microbial and may be present in an amount of 0.001 to 20%... Transglutaminase cross-links keratin by the acyl transfer reaction of a glutamine residue (acyl acceptor) and a lysine residue (amine donor). This reaction can occur intramolecularly or intermolecularly (see the BRENDA reference...) . One of ordinary skill in the art would have been motivated to combine the teachings of Richardson and BRENDA to produce a composition for cross-linking hair to maintain curl, because BRENDA teaches that protein molecules such as keratin in hair, which contain glutamine and lysine residues, may be cross-linked by transglutaminase alone..., and the skilled artisan would have recognized that the composition of Richardson, with or without the alkylamine compound, would have been used to cross-link hair. Additionally, as hair possesses a certain degree of curl, the application of transglutaminase to hair, described by Richardson, because of the cross-linking reaction, results in retention, enhancing and imparting of curl to hair.

Further regarding the action of transglutaminase on hair, Green discloses a composition comprising transglutaminase that is applied to hair. Transglutaminase is a cross-linking agent that cross-links corneocyte proteins that are present in the stratum corneum of the skin, hair or nails, thereby resulting in formation of a cross-linked layer....Kanebo also discloses a hair cosmetic composition comprising transglutaminase. Transglutaminase catalyzes the crosslinking reaction of free glutamine residues with lysine residues in the outermost layer of the hair....One of ordinary skill in the art would have been motivated to combine the teachings of Richardson with the teachings of Green or Kanebo to produce a composition for cross-linking hair to maintain curl, because Green teaches that transglutaminase alone may be applied to hair and that it crosslinks hair.

Richardson does not disclose the pH of the composition or applying heat to hair after applying the transglutaminase composition.

Dane discloses...that in creating curls and waves, disulfide bonds between the amino acids of keratin in hair are broken and new ones formed, thereby cross-linking the keratin in a new arrangement...Thus, one of ordinary skill...would have recognized that in designing a product to maintain or enhance the curl of permed hair, it would have been advantageous to have included an ingredient that can cross-link keratin, as disclosed by Robinson, Green, Kanebo or BRENDA, to maintain the new cross-linking pattern in hair...The skilled artisan would have been motivated to use the method of Richardson to maintain or enhance ...curl...because Richardson teaches that applying a transglutaminase composition can not only cross-link hair, it can also condition and

repair damaged hair by catalyzing the reaction of primary amines with superficial glutamines in hair keratin.

Regarding the pH of the transglutaminase composition, it is well known in the art that human transglutaminase has a pH optimum of 6...Thus, it would have been obvious to one of ordinary skill in the art that...an appropriate pH would have been approximately 6.

With respect to applying heat to a keratinous material after applying ...transglutaminase..., the hair may be subjected to heat with a hair dryer or blow dryer to style or reinforce curls. Thus, it would have been obvious to one of ordinary skill in the art that...the hair would have been subjected to heat to style the curled hair or to reinforce the curl.

Applicants respectfully traverse this rejection. In particular, it is believed that the rejection is based on an incorrect interpretation of the teachings of the primary reference, Richardson. While it is true that the document in question does disclose that transglutaminase can bond an alkylamine moiety to a glutamine residue, such as may occur on hair, the source of that alkylamine moiety is not a moiety found on hair, but rather is specifically an active material that is exogenously applied to the hair, whereby the transglutaminase assists in binding the active to a glutamine residue (see column 2, lines 48-50). Richardson does not disclose the cross-linking of any alkylamine moiety that naturally exists in hair, lysine or otherwise, to a glutamine residue in hair; there is simply no disclosure of the cross-linking of hair proteins, or the residues contained therein, with each other. On the contrary, the express purpose of the Richardson method is to bring external agents, such as antioxidants, conditioning agents or colorants, to the hair, skin or nails, and to bind these external agents to the glutamine residues of hair, not to bind amino acid residues within the hair to each other. In fact, to do so would be completely contradictory to the purpose of the Richardson method: glutamine residues that are cross-linked with other hair residues would then be unavailable to bind to the active agents, thereby completely defeating Richardson's purpose. Moreover, because the transglutaminase is functioning in achieving bonding of the active agent to the glutamine residue on the hair or skin, it is presumably not available to cross-link lysine and glutamine residues within a hair shaft. Thus, the disclosure of Richardson, rather than providing any motivation to use transglutaminase for hair curling, directly teaches away from the desirability of cross-linking hair amino acid residues with each other.

Without that motivation, and in fact, with the express disincentive to avoid cross-linking between glutamine residues and other amine residues within the hair, the basis of the remainder of the rejection fails completely. While the Examiner points in general to page 5, *et seq.*, as showing a collection of references relating to transglutaminase, the Examiner has failed to show where in that document there is a teaching that "protein molecules such as keratin in hair, which

contain glutamine and lysine residues, may be cross-linked by transglutaminase alone”.

Applicants have failed to locate this disclosure, and respectfully request that the Examiner show where such an express teaching can be found. However, even if it were to be found, there would be no motivation to combine it with the teachings of Richardson, which, as explained above, when read in its entirety, expressly teaches away from the notion of cross-linking glutamine residues with any amine residue within the hair. Thus, the combination of Richardson and BRENDA is not suggested, and even if the teachings were combined, would not suggest the use of transglutaminase for maintaining or imparting curl to hair.

The remaining cited references do not make any further contribution to rendering the claimed invention obvious. Green, like Richardson, is seeking to bind external agents, in this case, corneocyte proteins, to the skin, hair or nails. It is specifically noted, in column 1, lines 63-66, that the intention of the methodology described is to form crosslinks “between the amino acids of different proteins” (emphasis added). The end result of the method described is said to be to form a “protective layer” on the skin, hair or nails. No mention is made of using transglutaminase to influence curling of hair, and, as with Richardson, the linking of lysine and glutamine within a hair shaft would preclude the ability of the glutamine residues to bind with the corneocyte proteins, again defeating the avowed purpose of the method. Like Richardson, therefore, Green teaches away from crosslinking residues within the hair shaft.

Similarly, it appears that the Kanebo reference, although somewhat unclear as to what actually is occurring, is seeking to form an outer “protective layer” on the outer surface of hair, with the purpose of water retention. Water retention is certainly not the purpose of the present invention, and indeed, water tends to defeat the curling process rather than aid it. Again, while the abstract provided is not completely clear, this most closely resembles the Green reference in recommending the formation of an outer protective layer. There is unequivocally no disclosure whatsoever of transglutaminase being useful for imparting or retaining curl in hair.

Finally, the Dane reference unequivocally does not suggest that crosslinking within keratin shafts would be effective in maintaining curl or imparting curl. The document very specifically notes that all the types of bonds that occur in the hair, except for the disulfide bonds, are easily defeated by external forces such as water and humidity. While hydrogen bonds, ionic bonds and disulfide bonds are all mentioned, it is explicitly stated that the only bond that has any staying power is the disulfide bond. Glutamine and lysine are nowhere mentioned in the document, and it is well established that disulfide bonds in hair are the result of interactions between sulfur-containing amino acids; neither glutamine nor lysine is a sulfur-containing amino acid. Therefore, not only does the Dane reference not disclose anything at all with regard to

lysine and glutamine in hair protein, it renders completely unexpected and surprising the observation that a non-disulfide bond, such as would be formed between glutamine and lysine, would have any ability to hold the curl in hair.

In summary then, when the references cited are viewed in a light most favorable to the Examiner's arguments, they fail completely to suggest a method for imparting or retaining curl in hair by applying transglutaminase to hair, and in fact, to do so would completely obviate the cited references' intent in using transglutaminase in the first place. Since the basic technical premise of the rejection fails, and the primary subject matter of claim 1 is neither expressly disclosed nor remotely suggested in any one or all of the references, claim 1 cannot be found to be obvious in view of the cited combination of references. Likewise, all claims dependent thereon containing the basic limitation of claim 1, must also be considered unobvious. Withdrawal of the rejection is therefore respectfully requested.

Claims 1-18 have also been rejected under 35 USC §103(a) as being unpatentable over the same combination of references cited above, and further in view of product literature for E-Z Permanent Makeup. The rejection states that:

E-Z Permanent Makeup discloses that a permanent wave may also be applied to eyelashes...Accordingly, one of ordinary skill in the art...would have recognized that in designing a product to maintain or enhance the curl of permed eyelashes, it would have been advantageous to have included an ingredient that can cross-link keratin, as disclosed by Richardson, Green, Kanebo and BRENDA to maintain the new cross-linking pattern in the eyelashes resulting from the perm by applying a second cross-linking agent. The skilled artisan would have been motivated to use the method of Richardson to maintain or enhance the curl of permed eyelashes, because Richardson teaches that applying transglutaminase composition can not only cross-link keratin, it can also condition and repair damaged keratin by catalyzing the reaction of primary amines (which are present in keratin) with superficial glutamines in the keratin...

The deficiencies of the cited references have been addressed in great detail above, and will not be repeated here. In brief recap, and contrary to the Examiner's assertions, not one of the references even remotely suggests the desirability of cross-linking lysine and glutamine residues within the hair shaft, let alone suggests that applying transglutaminase could retain or impart curl to hair. There is simply no teaching to that effect in any of the references, and any assertion to the contrary by the Examiner is based on an incorrect reading of the references. The E-Z Permanent Makeup reference contributes nothing further in providing the missing teaching. First, there is nothing in the documentation provided by the PTO that teaches anything whatsoever with regard to permed eyelashes being the result of cross-linking keratin, so there is nothing to connect this document to any other document that discusses cross linking keratin. Indeed, the document specifically notes "Don't confuse this product with any other perm product used on our hair",

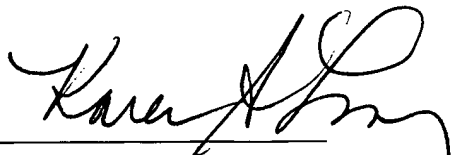
thus suggesting that, to the extent it teaches anything regarding the product, it should be assumed it is unique and unrelated to any other curling method. Thus, there is no motivation to combine this reference with any of the others cited, and even if combined, it would not suggest that transglutaminase would be useful for imparting curl or retaining curl in eyelashes, or any other type of hair. The Examiner's stated motivation for the combination is, as already noted, based on a misstatement of the disclosure of Richardson: this document does not disclose that transglutaminase can cross-link keratin, nor does it disclose that transglutaminase can condition and repair damaged keratin by catalyzing the reaction of primary amines in keratin with superficial glutamines in keratin. At best, Richardson discloses that transglutaminase can be used to bind an active component containing a primary amine (in the perfect example, a silicone conditioning agent that has been modified to contain a primary amine so it can be linked) to glutamine on hair. Nowhere does Richardson suggest that binding of primary amines existing in hair to glutamine residues result in conditioning or repairing damaged hair. Any conditioning resulting from the methodology of Richardson are expressly the result of the transglutaminase delivering a conditioning agent containing an amine directly to a glutamine; it unequivocally is not the result of the simple reaction between a primary amine group and glutamine. Therefore, for all the above reasons, the premise of this rejection completely fails, and must be withdrawn.

The office action does address arguments made by Applicants in the previous response. In view of the new rejections, the previously submitted arguments may be considered moot; in any case, the further arguments presented here, which directly address the newly stated rejection, clearly rebut any holding of obviousness of the present claims.

#### CONCLUSION

In view of arguments presented herein, claims 1-18 are believed to be in condition for allowance, and prompt issuance of a Notice of Allowance is respectfully solicited. The Examiner is encouraged to contact the undersigned by telephone if it is believed that discussion will resolve any outstanding issues.

Respectfully submitted,



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